REMARKS

Summary of Amendment and Status of Claims

Claims 1-47 are all the claims pending. Claims 1-7 are under examination and have been rejected. Claims 1-7 are amended, and support for the amendments to claims 1-7 can be found throughout the originally filed specification. Specifically, support for the amendments to claims 1-7 can be found in at least paragraph 0010 of U.S. Pre-Grant Publication No. 2004/0057956. Accordingly, no new matter has been added to the application. Applicant notes that claims 8-47 have been withdrawn from consideration at this time. Applicant reserves the right to file an appropriate continuing application filed during the pendency of this application to pursue non-elected subject matter.

Response to Rejection under § 101

The Office Action rejects claims 1-4 under 35 U.S.C. § 101 as allegedly being "non-statutory subject matter, a product of nature." *Office Action of 17 May 2007*, page 4. Particularly, the Actions alleges that the claims do not "point out any non-naturally occurring differences between the claimed antibodies and naturally occurring antibodies." *Id.*

Applicant has amended claim 1 to better capture the envisioned commercial embodiment. Applicant asserts that the claim amendment renders moot the rejection under 35 U.S.C. §101. Applicant requests reconsideration and withdrawal of this rejection.

Response to Rejection under § 112 for Indefiniteness

The Office Action rejects claims 1-7 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for "failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention." *Office Action of 17 May 2007*, page 5. Particularly, the Office Action alleges that "[i]t is not clear if the recitation, an 'isoform' of the amino acid sequence in claim 1 refers to an 'isoform' of ***the amino acid sequence comprising*** SEQ ID NO: 1 **OR** an '***isoform' consisting of SEQ ID NO: 1 itself***, which further comprises amino acid sequence." *Id.* (all emphases in original).

Applicant has amended claim 1 to better capture the envisioned commercial embodiment. Applicant asserts that the claim amendment renders moot the rejection under 35 U.S.C. §112, second paragraph. Applicant requests reconsideration and withdrawal of this rejection.

Response to Rejection under § 112 for Enablement

The Office Action rejects claims 1-7 under 35 U.S.C. § 112, first paragraph, as allegedly being unpatentable for "failing to comply with the enablement requirement." *Office Action of 17 May 2007*, page 5. Specifically, the Action asserts that "the instant specification does not provide sufficient direction or guidance to make and use antibodies encompassed by the breath of the instant claims." *Office Action of 17 May 2007*, page 6. In making the rejection, the Action states that phrase "'an isoform of the amino acid sequence' in claim 1 will be read as if it refers to an '***isoform' of SEQ ID NO: 1 itself***, which is defined in the instant specification … as differ[ing] in sequence from SEQ ID NO: 1 by 1-10 amino acids … ." *Office Action of 17 May 2007*, page 5 (emphasis in original).

Applicant has amended claim 1 to better capture the envisioned commercial embodiment. Applicant asserts that the claim amendment renders moot the rejection under 35 U.S.C. §112, first paragraph. Applicant requests reconsideration and withdrawal of this rejection.

Response to Rejection under § 102(e)

The Office Action rejects claims 1-7 under 35 U.S.C. § 102(e) as allegedly being anticipated by Rosen et al. (U.S. 2003/0054421; hereafter "Rosen") as evidenced by Bost et al., (Immunol. Invest. 1988; 17:577-586; hereafter "Bost"), Bendayan et al. (J. Histochem. Cytochem. 1995; 43:881-886; hereafter "Bendayan"), and the instant specification. Specifically, the Office Action concludes that "[g]iven the antibodies of Rosen, which are raised against a polypeptide having an amino acid sequence nearly identical to SEQ ID NO: 1 of the instant claims, and given that antibodies can be both specific and cross-reactive with antigens from different species . . . the antibodies of Rosen would inherently bind SEQ ID NO: 1." *Office Action of 17 May 2007*, page 8.

In making the inherency rejection, the Office Action alleges that Rosen teaches "antigentic epitopes of SEQ ID NO: 745, such as the epitope comprising residues 158-TEEEPQNDN-166 of SEQ ID NO: 745, … which is identical to SEQ ID NO:1, but for two mismatches." *Office Action of 17 May 2007*, page 7. The Office Action also alleges that Bost teaches antibodies which cross-react and in an attempt to establish "that the binding [of the antibody] to each protein is due to the presence of a homologous sequence in each protein of six amino acids, four of which are identical." *Office Action of 17 May 2007*, page 8. Further, the Office Action alleges that Bendayan stands for the proposition that "a monoclonal antibody can be highly specific for a given epitope and cross-reactive with antigens from different species or even distinct proteins not related to the original antigen." *Office Action of 17 May 2007*, page 8.

Applicant respectfully disagrees. Specifically, Applicant asserts that Rosen does not anticipate claims 1-7 as evidenced by Bost, Bendayan, and the instant specification because neither Rosen nor the cited references teach that the antibodies of present invention will "necessarily" bind SEQ ID NO: 1. "To establish inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference and that it would be so recognized by persons of ordinary skill." *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999) (citing *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* Notably the Federal Circuit recently elaborated on inherency in the complex arts. "Particularly when the science or technology is new or complex, a bare suggestion or hope that requires significant experimentation for implementation or verification is not an invalidating 'anticipation' of that which is ultimately achieved." *Pharmastem Therapeutics, Inc. v. Viacell, Inc.,* 2007 U.S. App. LEXIS 16245, 79 (Fed. Cir. July 9, 2007).

Claim 1 provides for an "antibody that recognizes the amino acid sequence comprising RSATEEEPPNDD of the α-subunit of $(Na^+ + K^+)$-ATPase enzyme." Rosen, however, does not teach an antibody that recognizes an amino acid sequence comprising RSATEEEPPNDD. Theorizing that the antibodies in Rosen "would inherently bind SEQ ID NO: 1" is the kind of probability or possibility that, by law, is insufficient to establish inherency. To be clear, Rosen does not inherently anticipate claim 1 because it is not certain that the antibodies discussed in Rosen will bind to SEQ ID NO: 1 of the present invention.

Indeed, it is known in the art that a substitution of even one amino acid can alter or inhibit the binding activity of an antibody or enzyme. (See Rudikoff *et al. Immunology* 1982; 79: 1979-1983 ("a single substitution–glutamic acid to alanine . . . was consistent with the loss in binding activity."); Witkowski *et al. Biochemistry* 1999; 38: 11643-11650 (replacement of the cysteine nucleophile with glutamine "completely inhibits the condensation reaction")). The art, therefore, teaches that even an single amino acid substitution may affect antibody binding. Thus, inherency can not be established, since there are well-documented instances of antibodies that are not cross-reactive between "homologous sequences." And as established earlier herein, inherency requires that the missing element is "necessarily present" in the cited art.

Further, one of skill in the art would readily recognize that Bost and Bendayan are inapposite to the present claims versus the cited reference. First, the Office Action alleges that Bost teaches that, "the binding to each protein is due to the presence of a homologous sequence in each protein of six amino acids, four of which are identical." (See Office Action, page 8). Both sequences involved in the cross-reactive Bost antibodies, however, involve sequences of identical length (LEHLLL versus LERILL) and only two adjacent amino acids were substituted within the amino acid sequence. Additionally, Applicant notes that the two amino acids substituted in Bost did not change the polarity or pH of the sequence, because a polar, basic histine was substituted for a polar, basic arginine at one site, whereas and a nonpolar, neutral leucine was substituted for a nonpolar, neutral isoleucine at the other site.

In contrast to situation presented in Bost, the sequences between the cited art and the present invention (RSATEEEPPNDD versus TEEEPQNDN), differ in length by three amino

acids, and the substitutions that the Office Action suggests as irrelevant to binding are not adjacent. Additionally, Applicant notes that the differences between the cited art sequences and the amino acid sequence represent fundamental changes in the characteristics of the amino acid side chains. Specifically, a polar glutamine is substituted for a non-polar proline and a neutral asparagine is substituted for an acidic aspartic acid. Thus, given that the art teaches that single amino acid substitutions can affect antibody binding, and given that the nature the amino acid differences between the cited art sequences and the sequences of the present invention are much more drastic than in Bost, an inherency argument can not be sustained.

The Office Action also asserts that Applicant has the burden of showing that the referenced antibodies in Rosen do not bind a polypeptide comprising SEQ ID NO: 1 and cites *In re Best*, *In re Marosi*, and *In re Fitzgerald et al.* for support. (*See Office Action*, page 8). Applicant asserts, however, that the cited case are distinguishable because these cases are applicable where inherency between the cited art and the claimed invention has been properly established. For example, the claims at issue in *Best, Marosi*, and *Fitzgerald et al.* were product-by-process claims where the claimed product was identical to the prior art product. In the present case, there is no evidence that the cited art antibodies will necessarily bind to the claimed antibodies. Further, and as discussed above, it does not follow that the prior art antibodies will necessarily bind to the amino acid sequence listed in the claims of the present invention.

Applicant requests reconsideration and withdrawal of the anticipation rejection under Rosen *et al.*

Response to Rejections under § 102(b)

Ball et al.

The Office Action rejects claims 1, 4 and 7 under 35 U.S.C. § 102(b) as allegedly being anticipated by Ball because Ball allegedly "teaches a polyclonal antibody raised against the peptide **EA**ATEEEP**Q**ND**N**, wherein the residues that are different between the polypeptide of Ball and SEQ ID NO: 1 are highlighted" and "as evidenced by Bost and Bendayan, the antibodies of Ball would inherently bind SEQ ID NO:1." *Office Action of 17 May 2007,* page 9 (emphasis in original).

Respectfully Applicant asserts that Ball, as evidenced by Bost and Bendayan, does not inherently anticipate claims 1, 4, and 7 for the identical reasoning listed above for Rosen. Furthermore, Applicant notes that, in this rejection, the Office Action is proposing that a four-amino-acid substitution would be irrelevant to antibody binding. Again, the nature of the amino acid substitutions are, from left to right, include substituting an acidic glutamic acid for a basic arginine, a polar serine for a non-polar alanine, a non-polar proline for a polar glutamine, and an acidic aspartic acid for a neutral asparagine. It is possible that the substitution of any one of these acidic, basic, or polar amino acid with an amino acid that is neutral or of opposing polarity opposing could greatly affect the reactivity of a polypeptide. Accordingly, inherency can not be established between the sequences of the cited art and SEQ ID NO:1. *See* Rudikoff *et al. Immunology* 1982; 79: 1979-1983 ("a single substitution–glutamic acid to alanine . . . was consistent with the loss in binding activity."); Witkowski et al. Biochemistry 1999; 38: 11643-11650 (replacement of the cysteine nucleophile with glutamine "completely inhibits the

condensation reaction")). Thus, there is no evidence to suggest the antibodies of Bost will necessarily bind SEQ ID NO: 1.

Applicant respectfully requests reconsideration and withdrawal of the anticipation rejection under Ball *et al*

Arystarkova et al

The Office Action rejects claims 1-3, 5 and 7 under 35 U.S.C. § 102(b) as allegedly being anticipated by Arystarkhova et al. (J. Biol. Chem. 1992 July 5; 567(19): 13694-13701) (hereafter "Arystarkhova"). Arystarkova "teaches a monoclonial body, "Vg4", which binds, at the very least, residues QAATEEEPQNDNL of human α1 Na^+ +K^+-ATPase." *Office Action of 17 May 2007,* page 10. The Office Action alleges that ,given "the extensive homology between rat and human polypeptides 96% identity across 1023 amino acids, indicating an overall conservation of structure, and further given that the residues to which the reference antibody binds, in particular residues EEEP which are critical for Vg4 binding, are conserved between rat and human, the reference antibody would bind to the claimed sequence." *Id.* (internal citation and parenthesis omitted).

Respectfully Applicant asserts that Arystarkova, as evidenced by Bost and Bendayan, does not inherently anticipate claims 1-3, 5 and 7 for the identical reasoning listed above for Rosen. Applicant notes that Arystarkhova does not expressly state that the Vg4 antibody would bind SEQ ID NO: 1. Applicant also notes that the Arystarkhova antibodies will not necessarily bind SEQ ID NO: 1, because even a change of a single amino acid may produce a significant change in binding affinity of an antibody. Applicant also notes that Bost and Bendayan are again

distinguishable for reasons already of record. Applicant respectfully requests reconsideration and withdrawal of the anticipation rejection under Arystarkova.

Response to Rejection Under § 103(a)

The Office Action rejects claims 1-3 and 5-7 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Arystarkhova in view of Rosen, Schwinger *et al.* (Circulation. 1999 Apr 27; 99(16): 2105-2112), Mohraz *et al.* (J. Biol. Chem. 1994 Jan 28: 269(4): 2929-2936), Bost, Bendayan, and the instant specification. Specifically, the Office Action alleges that "[g]iven the reference teachings that the Vg4 antibody binds to the extracellular sequence QAATEEEPQNDNL of human α1 Na^+ +K^+-ATPase, and enzyme involved in heart cell contraction that is down modulated in failing heart tissue, and further given that humanized antibodies for in vivo diagnostic use, it would have been obvious to one of ordinary skill in the art to prepare humanized Vg4 antibodies for the purpose of monitoring heart function in vivo." *Office Action of 17 May 2007,* page 12. The Office Action also asserts that "[o]ne of ordinary skill in the art would have had reasonable expectation of success in using the humanized Vg4 antibody to monitor α1 Na^+ +K^+-ATPase expression in vivo given that the epitope for this antibody is extracellular as taught by Arystarkhova and Mohraz." *Id.*

To begin with, the Office Action states that " it would have been obvious to one of ordinary skill in the art to prepare humanized Vg4 antibodies for the purpose of monitoring heart function in vivo." *Office Action of 17 May 2007,* page 12. Applicant, however, is not claiming humanized Vg4 antibodies in any of the pending claims. Rather, Applicant is claiming a

humanized antibody that binds to SEQ ID NO:1. Thus, the Office Action's conclusion is irrelevant to the claimed invention.

As to the remaining rejected claims, Applicant respectfully submits that the rejected claims are not obvious because (1) the combination of Arystarkhova, along with the cited references does not teach or suggest all the limitations of the claims and (2) the references cited do not suggest the desirability of such an alteration or combination of the cited art.

To establish *prima facie* obviousness of a claimed invention, all the cited references must recite all the claim limitations. *In re Royka,* 490 F.2d 981, 984 (CCPA 1974). For the reasons previously presented above, Applicant contends that neither Arystarkhova, Rosen, Ball, nor the other cited references teach or suggest all the claim limitations of the invention, either explicitly or inherently. In particular, these references do not expressly or inherently teach an antibody which is known to recognize the amino acids sequence listed in the claims. Thus, these references do not support a *prima facie* case of obviousness. Further, because the cited references do not teach all of the claim limitations, there can be no reasonable expectation of success in combining the cited references to arrive at the claimed invention.

For the reasons set forth above, Applicant maintains that the combination of the cited references, taken alone or in combination, fail to recite and teach all the limitations of the claimed invention. Accordingly, Applicant asserts that the combination of cited references fails to render obvious the claimed invention. Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection.

Request for Clarification on Priority Date

The Office Action states that the claims are "entitled to the benefit of priority of USSN 60/391,514, filed October 18, 2002." Applicant notes, however, that the filing date for USSN 60/391,514, to which priority is claimed, is June 25, 2002. Applicant respectfully requests acknowledgement of this claim of priority and priority date.

Conclusion

Applicant has amended claims 1-7 to better capture the envisioned commercial embodiments and has presented arguments regarding the lack of inherent anticipation of the claimed invention over the cited art. In view of the forgoing amendments and remarks, Applicant respectfully requests reconsideration and withdrawal of all of the above rejections. Applicant submits that this application is now in condition for allowance. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Todd B. Buck/

Todd B. Buck, Ph.D.
Registration No. 48,574

SUGHRUE MION, PLLC
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

WASHINGTON OFFICE
23373
CUSTOMER NUMBER

Date: 17 August 2007